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Toxicology in the 21st Century

Last August 28th, the President of the International Union of Toxicology (IUTOX), Professor Daniel Acosta Junior visited the School of Pharmaceutical Sciences at the University of Sao Paulo. Besides visiting some of our laboratories he ministered an enlightening seminar entitled Toxicology in the 21st Century. The seminar was attended by almost 50 people, among undergraduate and graduate students and professors. His speech was based on the changes of paradigm that must be in agreement with toxicology research in the 21st century.

The topic of the seminar was based on a published document in 2007 by the United States National Academy of Sciences and also, by the 3R's concept of **Russell** and **Burch** published in 1959 - "The Principles of Human Experimental Technique". Both statements indicate the need of changes in Toxicology research from animals *in vivo* to *in vitro* experimentation. Alternative test methods include any one that reduces, refines, or replaces an animal test. Non-animal test methods are *in vitro* or *in silico* methods and they are sometimes called replacement alternatives.

Until the last century, experimentation in toxicology was completely based in animals' research and the extrapolation from animals to humans was used for the risk assessment of chemicals. Most of the toxicity testing for hazard assessment are animal tests that were developed decades ago. End-points included signs, symptoms, morphological and clinical chemistry parameters. Most of the experiments were developed using high doses of exposure in short periods of time in order to guarantee that alterations would be observed. Dr Acosta included a discussion about advantages for replacing these animal toxicity tests by non-animal test systems. He also pointed out scientific, ethical and economic ones.

Replacement is not an easy task, especially for toxicologists as it represents a new paradigm: the development of methodologies that properly answer the questions of toxicity mechanisms with the use of a minimal number or even no animals. To facilitate the replacement of former tests with new ones, national and international authorities have developed standard processes and criteria for evaluating new toxicity test methods to determine whether they can replace an existing validated method.

To achieve this goal, mechanistic quantitative parameters should replace *in vivo* methods, which could only be achieved with the development of alternative methods.

Internationally, Europe (ECVAM), USA (ICCVAM), Japan (JACAM) and recently Korea created the Alternative Methods Center aiming at the development and validation of methods to answer questions of chemicals safety and efficacy. In Brazil this is a recent initiative marked by the creation of BRACVAM in 2011. Also in Brazil just recently the Ministry of Science and Technology instituted the National Network for Alternative Methods (Rede Nacional de Testes Alternativos - RENAMA) with the aim to develop, validate and certificate alternative technologies and methods to the use of animals for efficacy and safety testing of cosmetics, pharmaceuticals, pesticides and products for human health.

Although some *in vitro* methods have already been validated and can be applied mainly for cosmetics regulation purposes, there is still a great challenge for researchers, not only in the methodological aspect but mainly in the interpretation and extrapolation of *in vitro* results to real humans and environmental conditions.

Another issue is that most of the toxic alterations produced by chemicals to the general population are due to long term exposure and frequently to low doses. In this context the National Academy of Science of the United States document **Toxicity Testing in the 21st Century: a Vision and a Strategy** brings a new vision to toxicology testing and risk assessment. The document states the importance of toxicology testing to take advantage of the "advances on toxicogenomics, bioinformatics, systems biology, epigenetics, and computational toxicology transforming toxicity testing from a system based on whole-animal testing to one founded primarily on *in vitro* methods that evaluate changes in biologic processes using cells, cell lines, or cellular components, preferably of human origin" (http://www.nap.edu/catalog/11970.html).

Some animal testing will need to continue and moreover will not be abolished mainly considering *in vivo* toxicokinetics issues that could not be answered by cell systems alone. In this new approach animal testing will be mostly designed to answer questions raised by *in vitro* assays and not as a screening of chemicals toxicity as in the past.

International regulatory acceptance of a non-animal test method is the ultimate goal, which when achieved has a significant impact on reducing animal use in regulatory assessments. This new paradigm brings to researchers and regulators a great challenge. For researchers, the major concern is the development and validation of methods that could answer in a proper way the questions rose by regulators. As for regulators, there is a need to understand the new paradigm applied to human health risk assessment in order to ensure the safety use of chemicals by the population.

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